IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Dominik Meyer	)	Confirmation No. 2772
	)	
	)	Group Art Unit: 1616
Serial No.: 10/521,599	)	
	)	Examiner: Ernst V. Arnold
	)	
Filed: January 18, 2005	)	
	)	
Title: USE OF NEUROTOXIC SUBSTANCES FOR THE PRODUCTION OF A MEANS FOR THE TREATMENT OF JOINT PAIN AND METHOD FOR APPLICATION OF SAID MEANS	)	
	)	
Atty: Dkt.: LUS-15874	)	
	)	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' BRIEF (37 CFR § 43.37)

Sir:

This Appeal Brief is being filed in accordance with 37 C.F.R. §41.37 within two months of the Notice of Appeal, which was filed in this matter on October 16, 2008. The fee referenced in 37 CFR § 41.20(b)(2) in the amount of $270.00 is included with this submission. If any additional fees are due for this filing, please charge such additional required fees to our Deposit Account No. 18-0160, Our Order No. LUS-15874.

I. REAL PARTY IN INTEREST

Mestex AG, having a place of business at Bellerivestrasse 49, c/o Dominik Meyer, 8008 Zurich, Switzerland is the real party in interest and the assignee of all right, title, and interest to the invention throughout the world. An assignment from inventor Dominik Meyer to Mestex, AG was recorded on June 14, 2005 in the United States Patent and Trademark Office at Reel 16333, Frame 0444.

II. RELATED APPEALS AND INTERFERENCES

The application is not involved in an interference proceeding and there are no related appeals.

III. STATUS OF CLAIMS

The application was filed on January 18, 2005 together with a Preliminary Amendment that amended all 43 claims.

On May 4, 2007, applicant canceled claim 38 and 43 and amended all of the remaining claims in response to a restriction requirement. Claims 23-25 and 27 were thereafter withdrawn from consideration as being drawn to non-elected subject matter.

In an Amendment filed on January 7, 2008, applicant canceled claims 2, 10, 18-22 and 27, amended claims 1, 3-5, 11-17, 23-26, 28, 36 and 40-42 and added new claims 44-46 to the application.

In an Office Action mailed on April 18, 2008, the Examiner rejected claims 1, 3-9, 11-17, 26, 28-37, 39-42 and 44-46, and made the rejection thereof final.

On August 18, 2008, applicant filed an Amendment After Final that sought to amend claim 44. Specifically, applicant sought to amend claim 44 to change "the" mixture to read as "a" mixture in order to overcome a rejection under 35 U.S.C. §112, second paragraph.

In an Advisory Action mailed on September 22, 2008, the Examiner refused to enter the Amendment After Final on grounds that: (1) it did not place the application into better form for appeal by materially reducing or simplifying the issues for appeal; and (2) it would not place the application into condition for allowance.

Thus, claims 1, 3-9, 11-17, 23-26, 28-37, 39-42 and 44-46 are pending in the application, with claims 23-25 having previously been withdrawn from consideration. For the convenience of the Board, a copy of the pending claims is attached hereto in a Claims Appendix.

IV. STATUS OF AMENDMENTS

On August 18, 2008, applicant filed an Amendment After Final seeking to amend dependent claim 44 to address a rejection under 35 U.S.C. §112, second paragraph. In an Advisory Action mailed on September 22, 2008, the Examiner refused to enter the Amendment After Final.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention discloses and claims a method for treating post-operative joint pain. Such pain often originates in the area of the joint capsule or in the bone area close to the joint (page 1, lines 10-11). Applicant's method focuses on pain that emanates from nociceptive nerve fibers in the area near the joint (page 1, lines 14-15). It is known that local anesthetics can be injected into a diseased joint at conventional concentrations to alleviate such pain, but the pain relief is of limited duration and usually recurs (page 1, lines 15-18).

Applicant has surprisingly found that it is possible to obtain long-lasting joint pain relief by injecting an unconventionally high concentration of a local amide anesthetic dissolved in a biocompatible solvent into a post-operative joint space as a one-time application. When introduced in this manner, the local amide anesthetic diffuses to the sensitive nerve endings which directly or indirectly innervate the region of the joint, and damages these nerve endings such that long lasting pain relief is obtained (page 3, lines 5-18). The joint capsule or the synovial pouch retains the high concentration of the local amide anesthetic at the site of pain generation, making it possible to retain the unconventionally high concentration of local amide anesthetic at the site of pain than would otherwise be possible if the joint capsule or the synovial pouch were not present, while simultaneously leaving the cavity/nerve structures and other structures near the joint relatively unaffected (page 3, lines 10-16). The unconventionally high concentration of local amide anesthetic is neurotoxic/neurolytic to the sensitive nociceptive nerve fibers in the joint space, but surprisingly is not systemically toxic (page 6, lines 11-13).

The present patent application contains two independent claims. In an effort to comply with 37 C.F.R. §41.37(c)(1)(v), both independent claims are recited below, with bold, italicized parenthetical information added thereto to show where the claimed subject matter is described in the specification:

> Claim 1: A method for treating post-operative joint pain, the method comprising:
>
> providing an agent for treating joint pain comprising a neurotoxic substance dissolved in a bio-compatible solvent (***page 9, lines 12***), wherein said neurotoxic substance is an amide local anesthetic (***original claim 5***), and wherein said

amide local anesthetic is present in said agent for treating joint pain in a concentration whereby said agent for treating joint pain is predominantly toxic to nociceptive nerve fibers but not systemically toxic when injected into a post-operative joint space (***page 6, lines 11-12***); and

injecting the agent for treating joint pain into said post-operative joint space (***page 12, lines 1 and 6***) as a one time application (***page 6, line 10***) in an amount sufficient to entail neurolysis (***page 6, lines 12-13; original claims 38 and 43***).

Claim 43: A method for treating post-operative joint pain, comprising:

injecting an agent comprising a neurotoxic substance dissolved in a bio-compatible solvent (***page 9, lines 12***) into the intra-capsular region or into the joint synovial pouch of the pain-afflicted joint (***page 3, lines 10-16***) as a one time application (***page 6, line 10***) at a concentration entailing neurolysis (***page 6, lines 12-13; original claims 38 and 43***), wherein the neurotoxic substance is an amide local anesthetic (***original claim 5***) and is present in said agent in a concentration whereby said agent is predominantly toxic to nociceptive nerve fibers but not systemically toxic (***page 6, lines 11-13***).

The patentability of dependent claims 6, 7 and 11-17 is separately argued herein. Accordingly, in an effort to comply with 37 C.F.R. §41.37(c)(1)(v), claims 6, 7 and 11-17 are repeated below with bold, italicized parenthetical information added thereto to show where the claimed subject matter is described in the specification:

Claim 6: The method as claimed in claim 5, wherein the pH-lowering additive is a bisulfite (***page 5, line 24***).

Claim 7: The method as claimed in claim 6, wherein the pH-lowering additive is sodium bisulfite ($NaHSO_3$) (***page 5, line 25***).

Claim 11: The method as claimed in claim 5, wherein the amide local anesthetic is lidocaine at a concentration larger than 6 % (***page 5, line 4***).

Claim 12: The method as claimed in claim 5, wherein the amide local anesthetic is prilocaine at a concentration larger than 3 % (***page 5, line 5***).

Claim 13: The method as claimed in claim 5, wherein the amide local anesthetic is mepivacaine at a concentration larger than 5 %.

Claim 14: The method as claimed in claim 5, wherein the amide local anesthetic is bupivacaine at a concentration larger than 1.5 % (***page 5, line 7***).

Claim 15: The method as claimed in claim 5, wherein the amide local anesthetic is levobupivacaine at a concentration larger than 5 % (***page 5, line 9***).

Claim 16: The method as claimed in claim 5, wherein the amide local anesthetic is ropivacaine at a concentration larger than 2 % (***page 5, line 10***).

Claim 17: The method as claimed in claim 5, wherein the amide local anesthetic is etidocaine at a concentration larger than 2 % (***page 5, line 11***).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 1, 3-9, 11-17, 26, 40-42, 44 and 45 were properly rejected under 35 U.S.C. §103(a) as being unpatentable over Milligan et al. (Anaesthesia 1988, 43, 563-564) in view of Bawa et al. (US 6,261,547) and Goldenheim et al. (US 6,248,345) and Arias-Alvarez (US 4,657,764) and Strichartz (Regional Anesthesia and Pain Medicine, 1998, 23(1), 3-6).

B. Whether claims 1, 3-8, 11, 13, 26, 28, 35 and 40-42 were properly rejected under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (US 3,368,937).

C. Whether claims 1, 5, 28-37, 39 and 46 were properly rejected under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (US 3,368,937) in view of Goldenheim et al. (US 6,248,345) and Strichartz (Regional Anesthesia and Pain Medicine, 1998, 23(1), 3-6) and with respect to claims 34 and 37 Davis et al. (US 3,917,830) and with respect to claim 39 Herschler et al. (US 4,296,104) and with respect to claims 28-30 Oakes et al. (US 5,061,485) and with respect to claims 31 and 32 Mueller (US 5,002,761) and with respect to claim 36 Chasin et al. (US 5,942,241) and with respect to claim 33 Klaveness (US 5,242,683).

VII. ARGUMENTS

A. Claims 1, 3-9, 11-17, 26, 40-42, 44 and 45 Were Improperly Rejected Under 35 U.S.C. §103(a) as being unpatentable over Milligan et al. (Anaesthesia 1988, 43, 563-564) in view of Bawa et al. (US 6,261,547) and Goldenheim et al. (US 6,248,345) and Arias-Alvarez (US 4,657,764) and Strichartz (Regional Anesthesia and Pain Medicine, 1998, 23(1), 3-6).

1. Claims 1, 3-5, 8, 9, 26, 40-42, 44 and 45 (Grouped).

Milligan et al. discloses a double-blind study in which doses of 0.25% and 0.5% bupivacaine were injected into a knee joint after arthroscopy. Milligan et al. report in the summary that "intra-articular bupivacaine had no significant (post operative) analgesic effect in either concentration". In the discussion section, Milligan et al. note that the plasma levels were all determined to be below toxic plasma bupivacaine concentrations in man. The authors stated that while this might support a case for the use of higher concentrations of bupivacaine, they did not propose to undertake such a study for two reasons: (1) the bupivacaine molecules would likely traverse the synovium rapidly and thus cause plasma concentrations to increase (implying, of course, that there would be an increased risk that systemically toxic concentrations of bupivacaine could be achieved in the plasma); and (2) it would not likely be effective because the lack of any significant analgesic effect suggested that **the source of pain after arthroscopy was likely outside the capsule of the knee joint**.

The Examiner contends that in view of Milligan et al., one of ordinary skill in the art would have been motivated to inject bupivacaine into a post-operative joint space at higher concentrations than reported by Milligan et al. because Milligan et al. teach that a concentration of 0.5% provided little analgesia and because Milligan et al. noted that in view of the plasma levels, a case could be made for the use of higher concentrations. But this contention runs contrary to the clear teaching of Milligan et al. Milligan et al. does not suggest that one should use higher concentrations of bupivacaine to achieve a long-term analgesic effect. Milligan et al. clearly teaches away from that concept. Milligan et al. suggests that **the source of pain after arthroscopy was likely outside the capsule of the knee joint**. Thus, no person of ordinary skill in the art would be motivated by the teachings of Milligan et al. to inject bupivacaine at a higher concentration into the post-operative joint, and

would not have had any expectation that doing so would produce any beneficial effect.

The Examiner contends that Strichartz cures the deficiencies in the teachings of Milligan et al. Strichartz is an editorial discussing a case report authored by Choi YK et al., which was published in Reg. Anesth. Pain Med. 1998, 23: 96-100. After the final rejection, applicant submitted a copy of the Choi et al. case report for the Examiner's consideration. A copy of the Choi et al. case report is included in the Evidence Appendix for the Board's convenience.

In his Editorial, Strichartz notes that Choi et al. injected three (3) patients suffering from chronic painful conditions with a 5% lidocaine solution. The injection sites (which are described in the Choi et al. case report) were: a mandibular nerve (Case 1); occipital nerves (Case 2); and an intercostal nerve (Case 3). Strichartz noted that Choi et al. reported that relatively long-lasting pain relief was obtained in each case, but also indicated that pain returned in each case. The Choi et al. case report indicates that the mandibular nerve was injected on three separate occasions. **None of the three injection sites described in the Choi et al. case report was a post-operative joint space**. Thus, Choi et al. does not describe, teach or suggest injecting a high concentration of a local amide anesthetic into a post-operative joint space as a one time application.

The Examiner contends that one having ordinary skill in the art would have found it obvious to inject a 5% lidocaine solution into a post-operative joint space as a one time application in an amount sufficient to entail neurolysis (and would have increased the concentration of lidocaine to larger than 6% as claimed in claim 11) in view of Milligan et al. and Strichartz. Applicant respectfully disagrees. Milligan et al. suggests that the source of post operative joint pain is **likely outside the capsule of the knee joint** and that higher concentrations of local anesthetics would likely lead to systemic toxicity, and Strichartz questions whether a neurolytic explanation for the pain relief observed in the three cases discussed in the Choi et al. case report is plausible. Strichartz notes that the mechanism of pain relief described in the Choi et al. case report is uncertain, and that nerve lysis is unlikely to be the mechanism. Strichartz characterizes the procedures described in the Choi et al. case report as "futuristic, intriguing and exciting", and then concludes that more trials are necessary in order to "convince us that neurolysis with a commonly used anesthetic is no humbug."

The determination regarding whether an invention as claimed is obvious in view of the prior art must be made in accordance with the standards set forth in the Supreme Court's opinion in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ , 82 U.S.P.Q.2d 1385 (2007). In the *KSR* case, the Court made it clear that in order to reject a claim under 35 U.S.C. §103, there must be an explicit analysis explaining the apparent reason why a person of ordinary skill in the art would combine known elements described in the prior art in the way claimed. The person of ordinary skill in the art would have to see the benefit of making the combination. The person of ordinary skill in the art would have to recognize that it would improve similar devices or methods in the same way. The critical inquiry is whether the claimed improvement is more than the predictable use of prior-art elements according to their established functions. If it is, then the improvement is not obvious under 35 U.S.C. §103(a). In the present case, the analysis required by *KSR* requires a finding that applicant's invention, as claimed, is not obvious in view of Milligan et al. and Strichartz.

One having skill in the art would not have found applicant's invention as claimed obvious based on the combined teachings of Milligan et al. and Strichartz. Milligan et al. fairly teaches that the source of post operative joint pain is **likely outside the capsule of the knee joint** and that increasing the concentration of a local anesthetic in an solution injected into the post-operative joint would thus not likely be effective and would raise systemic toxicity concerns. And Strichartz questions whether a neurolytic mechanism can explain the three cases reported in the Choi et al. case report, none of which involved injections into a post-operative joint space. This clearly contradicts the Examiner's contention that the "concept of high concentrations of local anesthetics being neurolytic is known in the art and not anything new."

The additional references the Examiner attempts to combine with Milligan et al. (Bawa et al., Goldenheim et al. and Arias-Alvarez) do not overcome the deficiencies noted in the teachings set forth in Milligan et al. and Strichartz. None of these references suggest injecting concentrations of amide local anesthetics into post-operative joint spaces sufficient to entail neurolysis. Bawa et al. relates to an ophthalmic composition, which is an external optical application of an anesthetic drug to the eye. The mechanism employed in Bawa et al. is not neurolysis, but rather it is sustained release. It is wholly inapposite.

Goldenheim et al. discloses the use of local anesthetics in joints, but again does not disclose or suggest the use of neurotoxic concentrations of local anesthetics for any beneficial purpose. Goldenheim et al. discloses a sustained release composition. Again, the mechanism would be the same analgesia as commonly produced through the use of local anesthetics, and not neurolysis.

Arias-Alvarez teaches that sodium bisulfite can be taken orally to treat arthritis and epilepsy in humans. Arias-Alvarez does not teach a composition for injection into a joint space, and cannot be relied upon to cure the deficiencies in the teachings of Milligan et al. and Strichartz.

In view of the foregoing, the Examiner's rejection of claims 1, 3-5, 8, 9, 26, 40-42, 44 and 45 is clearly improper and should be reversed.

2. Claims 6 and 7 (Grouped).

As noted above, claims 6 and 7 claim applicant's method wherein the amide local anesthetic is used jointly with a pH-lowering bisulfite additive (claim 6) such as sodium bisulfite (claim 7). Arias-Alvarez teaches that sodium bisulfite can be taken orally to treat arthritis and epilepsy in humans. Arias-Alvarez does not teach a composition for injection, and thus no person having ordinary skill in the art would have found it obvious in view of the teachings of Arias-Alvarez to add sodium bisulfite to an injectable composition as taught by Milligan et al. or Strichartz. The Examiner's rejection of claims 6 and 7 is thus clearly improper and should be reversed.

3. Claims 11-17 (Grouped)

As noted above, claims 11-17 specify the minimum concentration of various amide local anesthetics in the solutions that are injected into the post-operative joint space in accordance with applicant's claimed method. Claim 11 specifies that the local amide anesthetic is lidocaine and that the concentration thereof is larger than 6%. Claim 12 specifies that the local amide anesthetic is prilocaine and that the concentration thereof is larger than 3%. Claim 13 specifies that the local amide anesthetic is mepivacaine and that the concentration thereof is larger than 5%. Claim 14 specifies that the local amide anesthetic is bupivacaine and that the concentration thereof is larger than 1.5%. Claim 15 specifies that the local amide anesthetic is lebobupivacaine and that the concentration thereof is larger than 5%.

Claim 16 specifies that the local amide anesthetic is ropivacaine and that the concentration thereof is larger than 2%. And, claim 17 specifies that the local amide anesthetic is etidocaine and that the concentration thereof is larger than 2%.

Milligan et al. discusses injecting **bupivacaine** into a post-operative knee joint at a concentration of **0.5%**. Strichartz (which discusses the Choi et al. case report) references that **lidocaine** at a concentration of **5%** was injected in three sites, none of which were post-operative joint spaces. Neither Milligan et al. nor Strichartz teaches the use of prilocaine, mepivacaine, lebobupivacaine, ropivacaine or etidocaine. However, the Examiner contends that one having skill in the art would have found it obvious to do so based on the teachings of Bawa et al. and Goldenheim et al., which teach an ophthalmic solution and an injectible solution, respectively, that contain conventional concentrations of various local anesthetics.

Applicant notes that no reference of record teaches or suggests a solution for injection into a post-operative joint space as a one time application, where the **lidocaine** concentration **is larger than 6%** as claimed in claim 11 or where the **bupivacaine** concentration **is larger than 1.5%** as claimed in claim 14. The "larger than 6%" lidocaine concentration claimed in claim 11 is at least 16.66% higher than the 5% lidocaine concentration mentioned in Strichartz (Choi et al.). And, the "larger than 1.5%" bupivacaine concentration claimed in claim 14 is at least 300% higher than the 0.5% bupivacaine concentration disclosed in Milligan et al. And there is nothing in the references of record that would suggest increasing the concentration of the two amide local anesthetics used in Milligan et al. and Strichartz to the minimum concentration levels claimed in claims 11 and 14.

Furthermore, the references of record do not teach a prilocaine concentration larger than 3% as claimed in claim 12, a mepivacaine concentration larger than 5% as claimed in claim 13, a lebobupivacaine concentration larger than 5% as claimed in claim 15, a ropivacaine concentration larger than 2% as claimed in claim 16 or an etidocaine concentration larger than 2% as claimed in claim 17. Because these specific local amide anesthetics were not utilized at all by Milligan et al. or Strichartz, in addition to identifying a prior art reference suggesting that these compounds themselves would be suitable for use in this application, the Examiner would also have to find something in the prior art that suggests that the concentrations claimed in the present application would have been obvious to one having skill in the art. There is no reference of record that would suggest that such compounds at such

concentrations. Thus, the Examiner's rejection of claims 11-17 is therefore improper and should be reversed.

B. Claims 1, 3-8, 11, 13, 26, 28, 35 and 40-42 (Grouped) Were Improperly Rejected Under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (US 3,368,937).

The Examiner also rejected claims 1, 3-8, 11, 13, 26, 28, 35 and 40-42 under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (U.S. Pat. 3,368,937). Macek et al. discloses an injectable steroid solution comprising an anti-inflammatory steroid and a local anesthetic. Macek et al. teach that the steroid solution can be administered by intramuscular, intrasynovial, intra-articular and soft-tissue injection.

The Examiner contends that Macek et al. teaches an injectable solution that consists essentially of a biocompatible solvent and from about 5 to 20 parts by weight of lidocaine or mepivacaine, which would be an unconventionally high concentration within the range claimed by applicant. The Examiner relies on what is recited in claims 1, 11 and 12 of Macek et al. for this proposition. Applicant respectfully submits that there is a clear error in claim 1, and that the specification and claims 11 and 12 demonstrate that the Examiner's rejection is improper. Macek et al. only teaches the use of conventional concentrations of lidocaine and mepivacaine (i.e., ≤1% by weight).

At col. 2, lines 4-6, Macek et al. states that the relative proportions, by weight, of the anti-inflammatory steroid (e.g., dexamethasone 21-phosphate) **to** lidocaine or mepivacaine is in the range of 1-20 to 4-1. This is an expression of the ratio of parts per by weight of two constituents of the injectable solution, and not an expression of actual parts by weight of such constituents in the injectable solution. This can be seen by reviewing the Examples of Macek et al., which specify the actual concentration of the constituents of the injectable solution:

> **Example 1**: 4 mg of dexamethasone 21-phosphate disodium salt and 8.93 mg of lidocaine base per 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 2.2; and the weight percent concentration of lidocaine in the injectible solution is **0.893%**);
>
> **Example 2**: 4 mg of dexamethasone 21-phosphate disodium salt and 8.93 mg of lidocaine base per 1 mL of water (Thus, the weight

ratio of dexamethasone to lidocaine is 1 to 2.2; and the weight percent concentration of lidocaine in the injectible solution is **0.893%**);

Example 3: 4 mg of dexamethasone 21-phosphate and 4.5 mg of lidocaine base in 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 1.1 and the weight percent concentration of lidocaine in the injectable solution is **0.45%**);

Example 4: 1 mg of dexamethasone 21-phosphate and 4.5 mg of lidocaine base per 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 4.5; and the weight percent concentration of lidocaine in the injectible solution is **0.45%**);

Example 5: 2 mg of dexamethasone phosphate and 5 mg of mepivacaine base per 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 2.5; and the weight percent concentration of lidocaine in the injectible solution is **0.5%**);

Example 6: 4 mg of dexamethasone phosphate and 10 mg of mepivacaine base per 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 2.5; and the weight percent concentration of lidocaine in the injectible solution is **1%**);

Example 8: 4 mg of dexamethasone 21-phosphate and 8.93 mg of lidocaine base in 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 2.23 and the weight percent concentration of lidocaine in the injectable solution is **0.893%**);

Example 9: 4 mg of prednisone phosphate and 8.93 mg of lidocaine base in 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 2.23 and the weight percent concentration of lidocaine in the injectable solution is **0.893%**); and

Example 10: 4 mg of hydrocortisone phosphate and 8.93 mg of lidocaine base in 1 mL of water (Thus, the weight ratio of dexamethasone to lidocaine is 1 to 2.23 and the weight percent concentration of lidocaine in the injectable solution is **0.893%**).

Example 7 differs from the other 9 Examples in that it does not disclose an injectable solution. As noted a col. 4, lines 56-62, Example 7 consists of a table that (bold underlined emphasis added):

illustrates the relative proportions of dexamethasone and lidocaine base, or dexamethasone and mepivacaine, which vary from 1-20 parts by weight of dexamethasone **to** 5-20 parts by weight of lidocaine base, or, in the case of mepivacaine, preferably 1-10 mg. per ml. when the

dexamethasone 21-phosphate is present in a concentration of 1-10 mg./ml.

Thus, Example 7 recites various ratios (expressed in parts per weight) of the steroid constituent as compared **to** the local anesthetic constituent (again, expressed in parts per weight). However, Example 7 does not specify the actual concentration of such constituents in parts per weight in an injectable solution. The actual concentration is expressed in milligrams per milliliter of water.

Claim 1 of Macek et al., upon which the Examiner relies, recites the weight ratio range between the steroid constituent and the local anesthetic constituent as set forth in Example 7. However, claim 1 of Macek et al. clearly includes an error. The first word of the fourth line of claim 1 of Macek et al. is incorrectly recited as "**and**" when it clearly should be the word "**to**". Claims 11 and 12 of Macek et al. confirm that only conventional concentrations of lidocaine and mepivacaine are contemplated (claim 11: 8.93 mg of lidocaine per 1 mL of water = **0.893% by weight**; and claim 12: 5 mg of mepivacaine per 1 mL of water = **0.5% by weight**).

The concentration of local anesthetics disclosed in Macek et al. is not the same as disclosed by applicant in the present application. And this makes sense, when one considers that Macek et al. teaches that the injectable solution can be injected intramuscularly, intrasynovially, intra-articularly and into soft tissue (see col. 1, lines 18-20). If one were to inject a solution containing 5-20 parts by weight (i.e., 5-20% by weight) of lidocaine intramuscularly or into soft tissue, one would reasonably expect to observe systemic toxicity. The Examiner's contentions regarding Macek et al. are simply not supported by the balance of such reference's teachings.

Macek et al. clearly does not teach or suggest anything to do with applicant's claimed method of treating post-operative joint pain. And thus one having ordinary skill in the art would not have been motivated to arrive at applicant's method, as claimed, in view of the teachings of Macek et al. Macek et al. teaches one how to combine a steroid with a local anesthetic in a concentration well-below where neurolysis would occur, such that the steroid solution is quick-acting and exhibits a long shelf-life.

C. Claims 1, 5, 28-37, 39 and 46 (Grouped) Were Improperly Rejected Under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (US 3,368,937) in view of Goldenheim et al. (US 6,248,345) and Strichartz (Regional Anesthesia and Pain Medicine, 1998, 23(1), 3-6) and with respect to claims 34 and 37 Davis et al. (US 3,917,830) and with respect to claim 39 Herschler et al. (US 4,296,104) and with respect to claims 28-30 Oakes et al. (US 5,061,485) and with respect to claims 31 and 32 Mueller (US 5,002,761) and with respect to claim 36 Chasin et al. (US 5,942,241) and with respect to claim 33 Klaveness (US 5,242,683).

The Examiner rejected claims 1, 5, 28-37, 39 and 46 under 35 U.S.C. §103(a) as being unpatentable over Macek et al. in view of Goldenheim et al. and Strichartz, and with respect to claims 34 and 37 in view of Davis et al. (U.S. Pat. 3,917,830), and with respect to claim 39 in view of Herschler (U.S. Pat. 4,296,104), and with respect to claims 28-30 in view of Oakes et al. (U.S. Pat. 5,061,485) and with respect to claims 31 and 32 in view of Mueller (U.S. Pat. 5,002,761) and with respect to claim 36 in view of Chasin et al. (U.S. Pat. 5,942,241), and with respect to claim 33 in view of Klaveness (U.S. Pat. 5,242,683). Macek et al., Goldenheim et al. and Strichartz have been discussed above. None of the references fairly teach injecting an agent comprising an amide local anesthetic in a concentration sufficient to cause neurolysis into **a post-operative joint space** for the purpose of achieving an analgesic effect lasting for many months to years.

Milligan et al. teaches injecting local anesthetics into joint spaces, but only in concentrations that would produce the known and expected short-term analgesic effect. Milligan et al. actually teaches away from applicant's invention.

Strichartz discusses three cases reported by Choi et al. in which higher concentrations of lidocaine were injected into sites **other than post-operative joint spaces**. Strichartz notes that Choi et al.'s mechanism is unknown, and that other testing would have to be conducted before any conclusions could be drawn. If that is the case, how could applicant's claimed method have been obvious in view thereof?

Macek et al. teaches one skilled in the art how to prepare a steroid/local anesthetic composition that is quick-acting and has a long shelf life. The concentration of local anesthetics in Macek et al. is conventional (i.e., well below the claimed concentration), and the Examiner is mistaken that Macek et al. teaches applicant's unconventionally high concentration of local amide anesthetics.

Goldenheim et al. teaches one skilled in the art how to prepare a sustained release anesthetic formulation. The composition according to Goldenheim et al. can contain many of the same constituents as are used in applicant's method, but Goldenheim et al. does not teach injecting a high concentration of a local amide anesthetic into a post-operative joint space.

None of the references cited by the Examiner, alone or in combination, fairly teach or suggest applicant's invention as claimed in claims 1, 5, 28-37, 39 and 46.

D. Rejection of Claim 44 Under 35 U.S.C. §112, Second Paragraph.

In the final Office Action, the Examiner rejected claim 44 under 35 U.S.C. §112, second paragraph, for lack of adequate antecedent basis. Applicant attempted to amend claim 44 in an Amendment After Final to address this error, but the Amendment After Final was not entered. Applicant reserves the right to file an amendment to amend claim 44 subsequent to a Decision on this appeal.

E. Provisional Double-Patenting Rejections.

Claims 1, 2 and 40-42 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting in the final Office Action as being unpatentable over claims 50 and 51 of copending application No. 11/722,779, claims 39-42 of copending application No. 11/722,857 and claims 94-96 of copending application No. 11/722,484. Applicant reserves the right to file terminal disclaimers to obviate the double-patenting rejections subsequent to a Decision on this appeal.

VIII. CONCLUSION

In view of the foregoing, it is respectfully submitted that claims 1, 3-9, 11-17, 26, 28-37, 39-42 and 44-46 are allowable over the prior art references of record, and a ruling from the Board to that effect is therefore respectfully requested.

Respectfully submitted,

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CLAIMS APPENDIX

Claim 1: A method for treating post-operative joint pain, the method comprising:

providing an agent for treating joint pain comprising a neurotoxic substance dissolved in a bio-compatible solvent, wherein said neurotoxic substance is an amide local anesthetic, and wherein said amide local anesthetic is present in said agent for treating joint pain in a concentration whereby said agent for treating joint pain is predominantly toxic to nociceptive nerve fibers but not systemically toxic when injected into a post-operative joint space; and

injecting the agent for treating joint pain into said post-operative joint space as a one time application in an amount sufficient to entail neurolysis.

Claim 2 (canceled)

Claim 3: The method as claimed in claim 1, wherein the amide local anesthetic is less neurotoxic to motor and propioceptive nerve fibers than to sensitive nerve fibers.

Claim 4: The method as claimed in claim 1, wherein the amide local anesthetic is used at a concentration larger than 4 %.

Claim 5: The method as claimed in claim 1, wherein the amide local anesthetic is used jointly with a pH-lowering additive.

Claim 6: The method as claimed in claim 5, wherein the pH-lowering additive is a bisulfite.

Claim 7: The method as claimed in claim 6, wherein the pH-lowering additive is sodium bisulfite ($NaHSO_3$).

Claim 8: The method as claimed in claim 5, wherein the pH-lowering additive is used at a concentration of at least 1 % by weight.

Claim 9: The method as claimed in claim 5, wherein the pH-lowering additive lowers the pH of the agent for treating joint pain to less than 3.5.

Claim 10 (canceled)

Claim 11: The method as claimed in claim 5, wherein the amide local anesthetic is lidocaine at a concentration larger than 6 %.

Claim 12: The method as claimed in claim 5, wherein the amide local anesthetic is prilocaine at a concentration larger than 3 %.

Claim 13: The method as claimed in claim 5, wherein the amide local anesthetic is mepivacaine at a concentration larger than 5 %.

Claim 14: The method as claimed in claim 5, wherein the amide local anesthetic is bupivacaine at a concentration larger than 1.5 %.

Claim 15: The method as claimed in claim 5, wherein the amide local anesthetic is levobupivacaine at a concentration larger than 5 %.

Claim 16: The method as claimed in claim 5, wherein the amide local anesthetic is ropivacaine at a concentration larger than 2 %.

Claim 17: The method as claimed in claim 5, wherein the amide local anesthetic is etidocaine at a concentration larger than 2 %.

Claims 18-22 (canceled)

Claim 23 (withdrawn): The method as claimed in claim 5, wherein the agent for treating joint pain further comprises a second different local anesthetic.

Claim 24 (withdrawn): The method as claimed in claim 23, wherein the agent for treating joint pain further comprises a third different local anesthetic.

Claim 25 (withdrawn): The method as claimed in claim 23, wherein the amide local anesthetic is bupivacaine and the second different local anesthetic is tetracaine.

Claim 26: The method as claimed in claim 5, wherein the amide local anesthetic is used in pure, enantiomeric form.

Claim 27 (canceled)

Claim 28: The method as claimed in claim 5, wherein a phenol or a pharmacologically acceptable phenol salt is used in addition to the amide local anesthetic.

Claim 29: The method as claimed in claim 28, wherein the phenol derivative is a cresol.

Claim 30: The method as claimed in claim 29, wherein the cresol is a chloro cresol selected from the group consisting of 2-chloro-m-cresol, 3-chloro-p-cresol, 4-chloro-m-cresol, 3-chloro-o-cresol, 6-chloro-o-cresol, 2-chloro-p-cresol, 5-chloro-o-cresol, 6-chloro-m-cresol and 4-chloro-o-cresol.

Claim 31: The method as claimed in claim 28, wherein the phenol derivative is a eugenol.

Claim 32: The method as claimed in claim 28, wherein the phenol derivative is a thymol.

Claim 33: The method as claimed in claim 1, wherein the agent for treating joint pain further comprises an x-ray contrast agent that contains gadolinium, iodine or barium in addition to the neurotoxic substance.

Claim 34: The method as claimed in claim 1, wherein the bio-compatible solvent is glycerin, and wherein the glycerin is used at a concentration of 10 to 95 % by wt in addition to the neurotoxic substances.

Claim 35: The method as claimed in claim 1, wherein steroids are used in addition to the neurotoxic substance.

Claim 36: The method as claimed in claim 1, wherein a vasoconstrictor selected from the group consisting of adrenaline, noradrenaline, phenylephrine and ornipressine, is used in addition to the neurotoxic substance.

Claim 37: The method as claimed in claim 1, wherein the neurotoxic substance is dissolved in a biocompatible solvent selected from the group consisting of glycerin, iophendylate and propyleneglycol.

Claim 38 (canceled)

Claim 39: The method as claimed in claim 1, wherein the agent further comprises dimethyl sulfoxide as a permeation enhancer.

Claim 40: A method for treating post-operative joint pain, comprising:

injecting an agent comprising a neurotoxic substance dissolved in a bio-compatible solvent into the intra-capsular region or into the joint synovial pouch of the pain-afflicted joint as a one time application at a concentration entailing neurolysis, wherein the neurotoxic substance is an amide local anesthetic and is present in said agent in a concentration whereby said agent is predominantly toxic to nociceptive nerve fibers but not systemically toxic.

Claim 41: The method for treating joint pain as claimed in claim 40, wherein the neurotoxic substance is a mixture of several amide local anesthetics and wherein a liquid volume of 0.1 to 150 ml of the agent is injected into the intra-capsular region or into the joint synovial pouch of the pain-afflicted joint.

Claim 42: The method as claimed in claim 41, wherein the nociceptive nerve fibers are rendered pain-insensitive by the mixture of several amide local anesthetics for at least 14 days.

Claim 43 (canceled)

Claim 44: The method as claimed in claim 40, wherein the nociceptive nerve fibers are rendered pain-insensitive by the mixture of several amide local anesthetics for at least 14 days.

Claim 45: The method as claimed in claim 1, wherein an analgesic is added to the neurotoxic substance.

Claim 46: The method as claimed in claim 1, wherein the bio-compatible solvent is polyethylene glycol.

EVIDENCE APPENDIX

On August 18, 2008, applicant submitted a copy of Choi et al., The Use of 5% Lidocaine for Prolonged Analgesia in Chronic Pain Patients: A New Technique, Regional Anesthesia and Pain Medicine 23(1): 96-100, 1998, for the record. The Choi et al. article was discussed in Strichartz (Regional Anesthesia and Pain Medicine, 1998, 23(1), 3-6), which is a prior art reference relied upon by the Examiner. A copy of the Choi et al. article is attached hereto for the Board's convenience.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.

Regional Anesthesia and Pain Medicine 23(1): 96–100, 1998

The Use of 5% Lidocaine for Prolonged Analgesia in Chronic Pain Patients: A New Technique

Young K. Choi, M.D., F.A.C.P.M., and Joseph Liu, M.D.

Background and Objectives. It has been found that 5% lidocaine with 7.5% dextrose causes irreversible conduction block in animal studies. Our case report subjects allowed us to observe the efficacy of 5% lidocaine for a prolonged analgesia *in vivo*. *Method.* After performing a diagnostic nerve block with 1% lidocaine, 5% lidocaine with 7.5% dextrose was injected into three patients with trigeminal neuralgia, postherpetic occipital neuralgia, and intercostal neuralgia, respectively. The patients were followed for one and a half years. Visual Analog Scale (VAS) scores and the side effects were recorded for each patient. *Results.* One patient received a trigeminal block and one patient received an occipital nerve block. Both patients reported immediate and complete pain relief lasting 14 and 8 months, respectively. One patient, given an intercostal nerve block, received immediate pain relief lasting 5 weeks. None of these patients exhibited any appreciable side effects or complications. *Conclusions.* Our observations suggest that 5% lidocaine may be used safely and effectively for the purpose of prolonged analgesia in selected patients with intractable chronic pain syndromes. *Reg Anesth Pain Med 1998: 23: 96–100.*
Key words: neurolysis, lidocaine, chronic pain.

Chronic pain syndromes can be caused by a chronic pathologic process of somatic or visceral structures or by prolonged dysfunction of the nervous system or have added psychological components (1). The nociceptive origin can often be controlled by oral pharmacologic agents and nerve block therapies. However, nerve blocks with local anesthetics may provide only short-term pain relief for patients, such as those with neuropathic or cancer pain. Subsequently, a neurolytic block of a peripheral or cranial nerve may be considered to alleviate the pain for a longer duration. A neurolytic block involves the use of neurolytic agents to disrupt nerves (2–5). The use of neurolytic agents to control chronic pain has been described for more than 100 years (6). Phenol and ethyl alcohol have been widely used as neurolytic agents; however, their neurolytic effect is variable in efficacy and duration of action. Complications, from the injection of those agents, that may also occur include neuritis, neuroma formation, and the sloughing of subcutaneous tissue, mucosa, or cartilage.

A solution of 5% lidocaine with 7.5% dextrose is an agent typically used for spinal anesthesia (7). Recently, it has been noted that this solution may be associated with a rare postblock effect—cauda equina syndrome (8–10). Some believed that this might be due to the direct exposure of the cauda equina to a high concentration of lidocaine. Lambert et al. used a solution of 5% lidocaine with 7.5% dextrose in desheathed bullfrog sciatic nerves

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Accepted for publication June 12, 1997
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and found that it caused irreversible conduction block in these nerves (11). We believed 5% lidocaine could provide longer lasting analgesia when used on peripheral nerves for better long-term control of intractable pain. We reported on our preliminary observations detailing the efficacy of 5% lidocaine as an alternative to neurolytic agents for a longer lasting analgesia in three patients with chronic pain.

Case Reports

Case 1

A 40-year-old white female with progressive multiple sclerosis presented to our pain center with constant sharp, shooting, stabbing, lancinating, and gnawing pain in her right cheek and chin area which began approximately 4 years previous. Her multiple sclerosis began 8 years ago, but the pain started after her wisdom teeth were extracted. Initially, she was placed on hydrocodone, amitriptyline, carbamazepine, and baclofen by a local neurologist, but all of these medications were subsequently discontinued because of adverse effects. She had also tried other types of antidepressants, anticonvulsants, anti-inflammatories, and analgesics as well, but they were ineffective in relieving her pain. She had no other medical problems. Examination revealed severe hyperesthesia and hyperalgesia in the region of the mandibular nerve and slight hyperesthesia and hyperalgesia in the infraorbital area of her right face. Touching her buccal mucosa triggered pain. Speech was laborious because of pain. Motor weakness of the right leg from multiple sclerosis was noted. With the impression of trigeminal neuralgia of the mandibular nerve (V3), she was placed on nortriptyline and choline magnesium trisalicylate. The patient also underwent psychological evaluation and treatment with cognitive-behavioral modalities. We performed a series of mandibular nerve blocks by injecting a mixture of 1% lidocaine and methylprednisolone. The Visual analog scale (VAS) (0 = no pain and 10 = maximum pain) was used to assess the efficacy of analgesia before and after the injection. Pain improved from VAS 10/10 to 3–5/10. However, the pain returned to VAS 10/10 in 3 weeks. The mandibular nerve block with 5% lidocaine was discussed with the patient, and an injection of 1 mL of 5% lidocaine with 7.5% dextrose was given incrementally after a trigeminal paresthesia was elicited by a nerve stimulator. The injection site was observed for 15 minutes to monitor any adverse effects such as swelling, redness, or itching. Immediate and complete pain relief, VAS 0/10, was noted in 1 minute without any significant side effects. Speech also improved with pain relief. The patient experienced slight numbness in the lower lip area 5 minutes after the injection, and it disappeared in 30 minutes. The patient's pain relief was ascertained after 1 day, 1 week, and every 3 months thereafter. There was no appreciable pain, numbness, burning, or motor weakness along with the mandibular distribution. However, the patient began to experience increasing pain along the maxillary division (V2) later. A diagnostic and 5% lidocaine block for infraorbital nerve were performed using the same technique as described earlier. Complete pain relief was obtained 1 minute after a 1 mL of 5% lidocaine with 7.5% dextrose injection. Visual analog scale changed from 8/10 to 0/10 and remained 0/10 thereafter. She was followed after 1 day, 1 week, 1 month, 3 months, and 6 months, and again she remained completely pain-free without any side effects. The patient returned to our pain center 14 months later because pain began to recur to VAS 10/10 in the V2 and V3 distribution, but the pain was more severe in the lateral side of the tongue and lower lip. A repeated block with 1 mL of 5% lidocaine and 7.5% dextrose was performed again to the mandibular nerve and infraorbital nerve. The patient currently reports minimal pain (VAS 0–1/10) and no side effects.

Case 2

A 67-year-old white male patient had chronic left occipitotemporal pain since having a herpes zoster infection two and a half years previous. The patient had been treated with various medications, including amitriptyline, nortriptyline, sinequan, zovirax, carbamazepine, dexamethasone, opioids, and anti-inflammatories, without any considerable benefits for his postherpetic neuralgia. The pain was constant, sharp, shooting, and burning in nature and was associated with allodynia, hyperpathia and/or dyesthesia. His past medical history was not remarkable. Examination showed significant hyperesthesia, hyperalgesia, numbness, and tenderness in the left occipitotemporal scalp area. We discussed further pharmacologic therapy with this patient; however, he declined. After instituting a psychological evaluation and therapy for cognitive-behavioral modification, relaxation training, and stress management, we performed a series of occipital nerve blocks and field blocks with 1% lidocaine and methylprednisolone, which only gave a few hours of pain reduction to a VAS of 3/10 each time.

Cryoanalgesia was discussed with the patient and cryoneurolysis of the occipital nerve was performed using Lloyd cryo-probe (Neurostat-Markll, Westco Medical Corporation, San Diego, CA); however, it only relieved the sharp pain for a few hours with VAS 2/10, and the patient reported the pain returned with a VAS of 10/10. Neurolysis with phenol was discussed and 1 mL of 6% aqueous phenol was injected incrementally using a nerve stimulator. After the phenol injection, the patient received good pain relief in 2 days with VAS 2–3/10 and was very satisfied. There was no additional numbness or skin sloughing. The patient returned to our pain center 3 1/2 months later with a recurrence of pain, VAS 10/10. A repeated block with 1 mL of 5% lidocaine and 7.5% dextrose was discussed and performed after a diagnostic occipital nerve block with 1% lidocaine. Good pain relief resulted and reduced the VAS from 9/10 to VAS 1–2/10 in 1 minute. The patient was followed after 1 day, 1 week, 1 month, 3 months, and 6 months thereafter. There were no side effects reported and satisfactory pain relief with VAS 2/10 lasted for the 8 months of follow-up.

Case 3

A 79-year-old white male patient had chronic intractable pain in his right antero-lateral chest wall for 13 months after a herpes zoster infection. The pain was constant, sharp, stabbing, and burning in nature and was associated with significant allodynia and hyperpathia. The patient tried capsaicin cream, zovirax, and various opioids without benefit, and the use of other medications such as antidepressants, anticonvulsants, and steroids was limited because he developed multiple allergic reactions and side effects. His past medical history included coronary artery disease with previous myocardial infarction, gynecomastia, and prostate cancer. Physical examination revealed hyperesthesia and hyperalgesia in the right-sided dermatomes of T2-T4. After a psychological evaluation and several treatment sessions, we performed a series of thoracic sympathetic blocks, and oral choline magnesium trisalicylate was added. Pain improvement was noted with VAS 2–3/10; however, the duration of pain relief became shorter after each treatment, changing from days to a few hours. Cryoneurolysis of the intercostal nerve was discussed and performed using a Lloyd cryo-probe at the level of T2-T4 under fluoroscopic guidance after a successful diagnostic block with 1% lidocaine. Satisfactory pain relief with a VAS of 1/10 lasted for 5 weeks; however, the original pain level of a VAS of 9/10 returned. We discussed and performed an intercostal nerve block injecting 1 mL of 5% lidocaine and 7.5% dextrose during fluoroscopic guidance. Good pain relief with a VAS of 1–2/10 was noted in 3 minutes without side effects. The patient experienced slight numbness for 15 minutes after the injection, but this resolved completely. The patient was followed after 1 day, 1 week, 1 month, and thereafter. The patient obtained good pain relief with a VAS of 1–3/10 for 5 weeks, and the pain has gradually returned.

Discussion

Neurolytic agents are sometimes advocated for interruption of pain transmission in selected patients with neuropathic or cancer pain. The pain from neuropathic origin or cancer is usually severe and may not respond to conservative treatments. Although the use of a neurolytic procedure for peripheral neuropathic pain is controversial, a chemical neurolytic block may be effective in alleviating pain, especially for elderly patients, patients in poor medical condition, and patients considered poor risks due to prior extensive surgical procedures. These blocks are simple to perform and are thus attractive to many physicians.

A variety of agents have been used to achieve chemical neurolysis, such as distilled water, hypertonic saline, ammonium salt, phenol, and ethyl alcohol (12). Phenol and ethyl alcohol have been most frequently used because of their predictable effects and infrequent side effects.

Phenol was first used for trigeminal neurolysis by Putnam and Hampton (13) in 1936. Injection of more than 5% phenol directly into the tissue causes protein coagulation and necrosis with nonselective blocks of nerve fibers, while injection of a lower concentration of phenol (<5%) may produce only a local anesthetic effect.

Ethyl alcohol was first used to treat trigeminal neuralgia in 1902. Concentrations of 50% and 100% ethyl alcohol can cause extraction of phospholipid cholesterol and cerebroside in the neuron and precipitation of mucoproteins and lipoproteins. This results in a separation of the myelin sheath and swelling of the Schwann cell and axon, and eventually destroys the nerve fibers nonselectively (14).

In addition to their neuronal effects, phenol and ethyl alcohol may cause tissue damage after injection, such as sloughing of subcutaneous tissue, mucosa, and cartilage. Ethyl alcohol may cause severe pain during injection and may produce neuritis with intense pain after injection, whereas phe-

nol typically does not cause significant pain on injection. Phenol causes numbness after injection and may require hours to days to show neurolytic effects.

Neurotoxicity from local anesthetics has been reported, but most often it appears to be caused by local anesthetic additives, such as bisulfite or benzyl alcohol. Local anesthetics per se were not often implicated in directly causing neurotoxicity (15). Others (16,17) indicated that at high enough concentrations, local anesthestics may cause endoneurial edema and Wallerian degeneration with Schwann cell injury and axonal dystrophy. Rarely it is also noted that the direct exposure of the cauda equina to a high concentration of lidocaine may contribute to the development of cauda equina syndrome. Lambert et al. noted that exposure of desheathed frog sciatic nerve fibers to 5% lidocaine with or without 7.5% dextrose resulted in an irreversible total conduction blockade (11). Strichartz et al. also found that 5% lidocaine appears to have neurotoxic potential in mammalian A and C fibers, and C fibers may be more susceptible than A fibers (18). It is unclear how 5% lidocaine caused an irreversible inhibition of neural condition. Lambert et al. concluded that it is not due to a residual local anesthetic effect or to membrane lysis. Other animal data (19) suggest that local anesthetic neurotoxicity might be concentration dependent, and some suggest local anesthetics be administered at the lowest possible effective concentration.

Using this background, we speculated that 5% lidocaine be used *in vivo* for the purpose of prolonged analgesia in chronic or cancer pain patients. The observation that 5% lidocaine did not cause histopathologic changes in neural tissue or surrounding tissue also suggested the drug may offer advantages for peripheral neurolysis. We successfully used 5% lidocaine with 7.5% dextrose, which is currently and commercially available as a spinal anesthetic agent for the purpose of prolonged peripheral nerve analgesia in three patients. Our data showed a variable duration with 5% lidocaine; however, it appears to last weeks to months. Two of our patients who showed trigeminal division paresthesia from a nerve stimulator received immediate, long lasting and complete pain relief, 14 and 8 months, respectively. One patient without paresthesia had a shorter duration of pain relief of 5 weeks. Further studies and follow-up are necessary to determine the typical duration of neurolysis. None of these three patients showed any subcutaneous tissue damage, neuritis, increased paresthesia following injection, and none exhibited pain on injection.

Conclusion

Five percent lidocaine was used successfully to minimize pain in three patients with chronic intractable pain, and it did not appear to cause significant side effects during or after injection. Five percent lidocaine may be considered as an alternative to neurolytic agents for prolonged analgesia. It is less costly to obtain, readily available, and appears to have minimal side effects. Even though only a limited amount of 5% lidocaine can be used for injection, we believe it can be applied to a variety of areas to produce prolonged analgesic effects. Further studies are necessary to assess the appropriate role for 5% lidocaine in managing patients with chronic pain.

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